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Datum 03.09.1999
Th/ka

Docket No. 99 D-0529
Guidance for Industry "Changes to an Approved NDA or ANDA" (June 1999)

Dear Sir/Madam

Please find hereunder the general comments from

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Contact person: Dr S Throm
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on FDA's Draft "Guidance for Industry: Changes to an Approved NDA or ANDA".

VFA appreciates that FDA will define more precisely the requirements for making and reporting manufacturing changes to an approved application.
VFA also welcomes that reporting requirements for certain changes have been reclassified into a less burdensome category.

Yet VFA suggests that FDA shall publish the BACPAC II Draft for Industry comment purpose before progressing with this guidance. After evaluation of the comments a guidance should be published which includes BACPAC I and BACPAC II. Finally, based on "BACPAC" the Guidance for Industry "Changes to an Approved NDA or ANDA" should be filed.

Rationale: The Draft Guidance "Changes to an Approved NDA or ANDA" includes proposals for API-related post-approval changes procedures and requirements which are very similar to those which were included in the BACPAC I Draft.

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The new Draft Guidance also covers the scope of the yet to be issued BACPAC II Draft. The contents of the Draft Guidance indicates that comments received by FDA from industry on the BACPAC I Draft have not yet been taken into account during its drafting.

Therefore a copy of our previously submitted comments on the BACPAC I Draft Guidance are annexed for your convenience.

The Draft Guidance includes proposals for API-related post-approval changes procedures and requirements. It is not always clear whether or not some requirements are applicable to APIs or intermediates. A strict differentiation between drug products and APIs would be helpful. This would allow FDA to define separate categories of changes for APIs.

Only a change in the quality of an API (impurity profile and/or physical properties) can have the potential to adversely affect the identity, strenght, quality, purity or potency of a drug product and thus influence the safety or efficacy of the drug product. The quality of an API is clearly defined by its specification in combination with the synthetic route. The modern test methods are suitable to detect impurities far below a level which is relevant to the safety of the product. Therefore the equivalence of the quality of an API before and after a change can be proven. Only in cases where there is a risk that new impurities can be formed which have a potential not to be detected with warrantable analytical effort, the change should be classified as a major change as defined in the Draft Guidance.

VFA will publish a proposal for the classification of changes in the synthesis of APIs which is based on this principle within the next few months.

Sincerely yours,

Dr. Siegfried Throm
Production, Quality, Environment

VERBAND FORSCHENDER ARZNEIMITTELHERSTELLER E.V.

Comments of Verband Forschender Arzneimittelhersteller e. V. (VFA) on Draft Guidance for Industry on BACPAC I: Intermediates in Drug Substance Synthesis; Bulk Actives Post-approval Changes: Chemistry, Manufacturing and Controls (CMC) Documentation; Notice of Availability Appearing in the Federal Register of 30 November 1998 (63FR5793) - Docket No 98D-0995 -

Genereal comments

We understand that the changes covered by BACPAC I only encompass changes in the information filed in the approved application.

It should be sufficient to prove the equivalence by comparing three postmodification batches to three recent premodification batches. Equivalence is demonstrated if impurities are within the stated limits of the specification or if not specified at or below the upper statistical limit of historical data. When equivalence is proven before the final intermediate filing the change in an annual report should be sufficient.

All BACPAC I changes should be reported to the FDA and the drug product manufacturer. However the drug product manufacturer should not be obliged to file a CBE supplement or an annual report for such changes, since the drug substance quality is not affected. Furthermore, if an API intermediate manufactuer supplies other API manufacturers or drug product manufacturers it does not make good economic or scientific sense for the FDA to have to assess several NDAs which all reference the same change made by one API manufacturer in one DMF.

Changes made prior to the final intermediate, reporting by an Annual Report is suggested for all cases where impurity equivalence is demonstrated before or at the final intermediate. For those changes in which the evaluation is carried out on the drug substance, a Change Being Effected supplement is suggested.

Specific comments

Page 2, line 17-20:
Postapproval changes affecting (1) ~~synthetic peptides~~, (20) olingonucleotides, (3) radio-pharmaceuticals, or (4) drug substances derived exclusively by isolation from natural

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sources or produced exclusively by procedures involving biotechnology are not addressed in the document.
Synthetic peptides should be within the scope of BACPAC I as there is not principle difference between peptides and other drug substances produced by organic synthesis.

Page 4, line 95-97:
~~For example, if the drug substance is a mixture of isomers, then the same quantitative mixture should be obtained after the change.~~
This sentence should be deleted as it is covered by the general equivalence requirement.

Page 5, line 123-124:
The level of impurities should be assessed by comparing three postmodification batches to three ~~ten~~ premodification ~~commercial~~ batches.
(see general comments)

Page 5, line 128-130:
The impurity profile will be considered equivalent after a given change if at least three postmodification batches of either an isolated (or in situ, if appropriately justified) intermediate or the drug substance are evaluated and the test data demonstrate that for:
The demonstration of equivalence may take place at an in situ intermediate if appropriate justification is provided.

Page 5, line 137-138:
Existing impurities, including residual solvents if relevant~~, are at or below the upper statistical limit of historical data~~ are within the approved specification or, if not specified, are at or below the upper statistical limit of historical data.

Page 5, line 139:
Total impurities are within the stated limits, or, if not specified, are at or below the upper staitstical limit of historical data.

Page 6, line 149-150:
Existing impurities, including organic solvents if relevant, are within the stated limits, or, if not specified, are at or below the upper statistical limit of historical data.

Page 6, line 159:
~~In situ intermediates are generally not appropriate for demonstrating equivalence.~~
In situ intermediates, if appropriately specified, should be treated as isolated intermediates.

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Page 7, line 200:
Conformance to historical ~~particle size distribution profile~~ specification.

Page 8, line 227-229:
Site changes within a single facility or within a contiguous campus that fall within the scope of sections IV.A and IV.A1 need not be filed with the Agency, and equivalence testing as described in this document need not be carried out.

Bonn, 3 May 1999, Th/sch
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